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The impact of co-morbid Severe Mental Illness and HIV upon mental and physical health and social outcomes: a systematic review

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Our aim was to review the evidence related to the impact of co-morbid severe mental illness SMI (schizophrenia, schizoaffective and bipolar disorder) and HIV upon mental health, physical health and social outcomes. We carried out a systematic review of scientific evidence, searching online databases (MEDLINE, PsychInfo, EMBASE, Global Health and Scopus) for studies between 1983 and 2017 using search terms for SMI and HIV. Studies were included if they compared health or social outcomes between people living with co-morbid SMI and HIV and people living with either: a) HIV only; or b) SMI only. Outcomes of interest were: mortality, health service use, HIV/SMI-related, co-morbidities, and social outcomes. We identified 20 studies which met our inclusion criteria. Although studies were generally high quality, there was heterogeneity in both selection of outcomes and choice of measure. It was therefore difficult to draw strong conclusions regarding the impact of co-morbid SMI and HIV across any outcome. We found little evidence that co-morbid SMI and HIV were associated with lower levels of treatment, care or poorer clinical outcomes compared to people living with SMI or HIV alone. However, mortality appeared to be higher among the co-morbid group in two out of three studies. Physical and mental co-morbidities and social outcomes were rarely measured. Limited data mean that the impact of co-morbid SMI and HIV is uncertain. In order to develop evidence-based guidelines, there is an urgent need for further research. This may be realized by exploring opportunities for using data from existing cohort studies, routinely collected data and data linkage to investigate important questions relating to this neglected but potentially important area.

Systematic review; schizophrenia; bi-polar disorder; schizoaffective disorder; HIV; comorbidity

Introduction

Despite availability of highly effective treatments, both HIV and SMI are associated with high levels of avoidable morbidity and mortality [1, 2]. Although HIV and SMI are serious chronic conditions, when optimally managed individuals are able to live largely free of disability and illness. However, there is now significant evidence of health inequalities associated with each condition, resulting in greatly increased risk of mortality for some groups. People living with SMI have double the risk of mortality compared to the general population (pooled relative risk=2.2 [3] and starting antiretroviral therapy (ART) with a CD4 count of less than 350 cells/µL is associated with 15 years loss of life [1]. A recent systematic review estimated that the rate of HIV among people living with SMI in the USA was ten times that of the general population, at 6.0% versus 0.6% [4]. The pooled prevalence for studies carried out in African settings was even higher at 19%, suggesting that the global burden of people with SMI and HIV could be significant [4].

Very little is known about the impact of SMI and HIV co-morbidity. We could identify no previous systematic reviews about health and social outcomes of people living with SMI and HIV. Research indicates that similar challenges inhibit positive patient outcomes across both conditions. Both conditions require high levels of adherence for treatment to be effective[5]. For people with schizophrenia, rates of partial adherence or non-adherence are estimated to be at least 40-50%, with rates worsening over time [6]. Rates for adherence to ART tend to be higher; a recent systematic review identified pooled ART adherence rates of 86% for people living in lower income countries and 68% for people living in higher income countries[7]. Some of the same barriers apply to adherence to medication for both conditions: alcohol and substance use; side effects; lack of social support; difficulties accessing treatment; transportation; resources to buy medication; patient experience of the health services including relationships with staff [6, 8]. Although people with SMI have much higher rates of death from

suicide and other unnatural causes, the vast majority of excess mortality is due to those conditions which are the most common cause of death among the general population[9, 10]. Similarly, although AIDS-related causes account for around a third of deaths among people living with HIV/AIDS [11], PLHA are at higher risk of non-communicable diseases (NCDs) such as cancers, liver disease and cardiovascular disease which account for 40% of deaths [11]. As in the general population, risk factors are multifactorial and include lifestyle factors such as smoking, alcohol and drug-use[9]. However, both long-term ART use and use of anti-psychotics are associated with metabolic changes linked to NCDs. Finally, research suggests that the accumulation of difficulties associated with living with HIV or with SMI result in worse social outcomes for some of those affected. A large body of evidence suggests that between 25 and 60% of people living with SMI have substance use or dependency on drugs and alcohol [12, 13] and that this co-morbidity is associated with multiple challenges regarding management, including recurrent presentation at services, higher rates of social problems and relapse [13].

Given the evidence of risk of poor outcomes for each condition [10, 14] we would argue that the lack of research in this area is a significant concern. There are currently no internationally agreed guidelines to support the management of co-morbidity [15]. Given the challenges associated with the management of each condition; additional complexity associated with co-morbidity is likely to be significant. However, excess risk associated with co-morbidity is likely to be modifiable [9]. The aim of this systematic review is to synthesize existing evidence, using the syndemic paradigm to frame our work providing a platform for further research and possible guideline development.

Methods

Search Strategy

The Preferred Reporting items for reviews guideline was adopted in this study [16]. The protocol for the study was registered with an international prospective register for systematic reviews- PROSPERO (http://www.crd.york.ac.uk/prospero/display_record.asp?src=trip&ID=CRD42016037284).

Our scoping searches revealed the relatively small size of the evidence-base, we therefore agreed upon a pragmatic decision to group together study participants with a diagnosis of schizophrenia, schizoaffective disorder or bipolar disorder as having "severe mental illness" (SMI). This categorization is commonly used by researchers in this area and has a strong theoretical basis, given that these are the most frequently diagnosed disorders which are likely to result in persistent, disabling illness resulting in a need for specialized psychiatric treatment (in-patient and out-patient) in settings where these services are available [17, 18]. On the 21st of June 2016, we searched five online databases including MEDLINE, PsycINFO, EMBASE, Global Health and Scopus. The search was updated on the 19th June 2017 to include studies conducted after the initial search. The search terms 'severe mental illness' (its synonyms and related terms including schizophrenia*, bipolar disorder, psychosis, schizoaffective and severe mental disorder*) and 'human immunodeficiency virus'. We also searched within the references of the studies identified by our search of databases. See Table 1 for eligibility criteria. The rationale for the date of publication criteria is derived from the date of publication of the first study to identify HIV as the cause of AIDS [19].

Data collection and analysis

The study selection was based on eligibility criteria set out in the protocol registration. The search was conducted by IE and RM and the results from the databases exported to Endnote X7, which was also used to eliminate duplicate studies. An initial screening of abstract and titles was conducted by IE using the eligibility criteria and was double-screened by RP. The selected articles for full text review were

retrieved and reviewed by IE while RM, DO and CT independently reviewed the identified articles. A final list of 20 articles was selected by consensus by IE, RM, DO and CT (see Figure 1).

Data including author, year of publication, country of publication, study design, study population and background, outcome variables and statistical methods were extracted into an excel sheet by IE and RM. The extracted material was reviewed together by IE, RM, DO and CT in three review sessions. Quality assessment of studies was conducted by IE using the Quality Assessment Tool for Systematic Reviews of Observational Studies (QATSO)[20] as used by Hughes and colleagues [4]. Domains and rules for scoring were as follows: clear definition of SMI/HIV population (No=0,Yes=1);Response rate (≤60% or not reported=0, >60%=1; whether study controlled for confounding through matching, restriction or adjustment (No/if descriptive=0,Yes=1); sample size (<200 participants=0,≥200 participants=1), giving a score of 0-4. Outcomes of quality assessment are described in Table 2. We did not exclude studies on the basis of quality.

The study was exploratory and the studies included were heterogeneous in terms of design, populations, selected outcomes and measures. We therefore conducted a narrative synthesis based on the study objectives.

Results

We identified 20 studies in total which met our inclusion criteria (see Table 2) and the total number of study participants was 8,788,290 (sample size ranged from 27 to 5,901,621). However, some studies used the same data sources: eg. One group of authors carried out cross-sectional followed by longitudinal analyses of participants in HIV Research Network Sites [21, 22]. In the following cases, overlap in samples cannot be ruled out: HIV-only comparison groups were obtained from the HIV Costs and Services Utilisation Study for two studies [23, 24]; two studies used Veteran's Health Association

data (analysing different outcomes) [25, 26]; two studies used Medicaid data from a similar time period [27, 28], (a further study used Medicaid data from a different time period- [29] and a group of authors carried out complimentary analyses- different time periods, new healthcare cost estimates, using Medicaid data [30, 31]; two studies recruited participants from the same hospital site (Butabika National Referral Hospital, Uganda) during similar time periods but analysed different outcomes [32, 33]. Thirteen studies were cohorts while the remaining seven were cross-sectional. Eight studies compared outcomes between people living with SMI and HIV and those living with SMI only [25, 27, 32, 34-38] and 16 studies compared outcomes between people living with SMI and HIV and those living with HIV only [21, 23, 24, 27, 29, 35-37, 39-46]. 17 studies were carried out in the USA, six of which consisted of analysis of health insurance claims records data [25, 27, 29, 34, 36, 37]. Studies from outside of the USA included: a large population-based cohort study from Denmark [35] using linked registries; two clinical cohort studies from Uganda [32, 43]; a small clinical study carried out in Italy [46].

A high proportion of studies selected for inclusion were judged to be of good quality (81% (n=16)) scoring 3-4 overall on the quality assessment, with large sample sizes, good retention and clear definition of exposure groups (see Table 2). The most common reason for scoring less than the maximum of 4 was no adjustment for confounders.

Outcomes measured included the following: mortality, suicidality, AIDS-defining illness, ART use/discontinuation/adherence, health service use, costs, receipt of care (as described below and in Table 2).

Mortality

Three studies examined mortality. Two studies found that people with SMI and HIV had an elevated risk of death compared to those living with HIV alone (MMR=76.5, 95% CI=44-122, compared to HIV only MMR=47.2, 95% CI=41-54 [47]; and adjusted hazard ratio=1.40, 95% CI=1.11-1.77)[26]. In the same

study, although risk of death was higher for people living with schizophrenia compared to those without a mental disorder, risk of death was further elevated for the group with SMI and HIV across the two time periods considered[26]. However, in their analysis of Medicaid records from Maryland USA Chander et al found no difference in mortality between people living with SMI and HIV and those living with SMI alone [28].

Suicidality

Two studies examined suicidality. A cross-sectional study carried out among psychiatric inpatients at an urban hospital in the USA found that those patients with SMI and HIV were more likely to have suicidal ideation [38]. However, a larger longitudinal study carried out using a national inpatient database found that although people living with psychosis and HIV had no increased risk of suicide attempts/self-inflicted injuries compared with those without a diagnosis of SMI (AOR=1.28, 95% CI=0.84-1.96); those with psychosis alone had elevated odds of suicidality (AOR=1.73, 95% CI=1.64-1.82)[48]. In the same study, a similar pattern was found for non-adherence to medical treatment.

HIV-related factors

Four studies examined AIDS-defining illness. None of the three studies carried out in the USA found a difference in the incidence of AIDS-defining illnesses between people with SMI and HIV and those living with HIV alone [26, 28, 45]. However, in their Ugandan sample, Nachega et al found that people with SMI and HIV were more likely to be diagnosed with HIV-related dementia and wasting syndrome compared to those with HIV alone, although there was no difference in the odds of having toxoplasmosis[33].

Nine studies examined various factors related to ART use. Three out of four studies found no evidence of a difference in ART use between people living with SMI and HIV and those living with HIV alone [23,

29, 45]. The exception to this was a small study carried out in Italy (n=27) which found that those with new-onset psychosis were less likely to be using ART than those with HIV only [46]. Although Himelhoch et al (2007) found no evidence of a difference in ART use between those with SMI and HIV and those with HIV alone, they did find that those with SMI and HIV and co-morbid Injecting Drug Use (IDU) were less likely to be in receipt of ART than those living with HIV alone (AOR=0.52 (95% CI=0.41-0.81) [22]. In a Danish study using linked data registries, during the earlier study period people living with HIV and schizophrenia were found to be less likely to initiate ART (IRR=0.42, 95% CI=0.13-0.99) during the later period there was no evidence of a difference between groups [47]. In their study using data from HIV Research Network sites, Himelhoch et al (2009) found that people with SMI and HIV were less likely to discontinue ART than the HIV alone group during the first two years of treatment only [49]. Among Ugandan patients, Nachega et al (2013) found that SMI and HIV was associated with increased odds of discontinuation of ART (adjusted hazard ratio=1.58, 95% CI=1.06-2.33)[33]. An analysis of New Jersey Medicaid records found there was no evidence of a difference in time on ART between those with SMI and HIV and HIV alone [29]. Finally, a small study which compared adherence to ART between people with bi-polar disorder and HIV and HIV alone found that adherence was worse for the bipolar and HIV group across both measures administered [42].

Health service use and associated costs

Seven studies examined health service use, costs or receipt of HIV care. Analysis of data from HIV Research Network sites in the USA showed that people living with SMI and HIV had increased odds of inpatient medical hospitalisation compared to HIV alone (AOR=1.70, 95% CI=1.34-2.15) [22]. Those with IDU in addition to SMI and HIV had further increased the odds of an inpatient episode (AOR=2.22, 95% CI=1.64-3.01), compared to those with HIV alone[22]. Contrastingly, in an analysis carried out using data from a multisite study, Rosenberg et al (2005) found that people with SMI and HIV had a lower mean

number of hospitalisations, as compared with people living with SMI alone [25]. In the same study, the SMI and HIV group were also less likely to have had recent experience of being arrested, jailed or homelessness compared to those with SMI alone. In a series of studies examining health service use and associated costs among Medicaid patients in Philadelphia, Rothbard et al consistently found that people living with SMI and HIV had higher rates of health service use than the SMI alone and HIV alone groups and consequently higher associated costs[27, 36, 37]. Fremont et al (2007) found that people with SMI and HIV were more likely to report problems with HIV related medical care [24]. Bogart et al found that people living with SMI and HIV were as likely as people with HIV alone to receive adequate HIV monitoring [23].

Other co-morbidities

Nine studies examined other co-morbidities, most commonly drug use (n=6). Findings suggest that compared to people living with HIV alone, people with SMI and HIV are more likely to have a history of IDU [21], report recent heroin/cocaine use [24] or abuse drugs and alcohol [40]. Drug and alcohol-related disorders and disability were also more common among people with SMI and HIV compared to people living with SMI alone [30]. Two small studies found that people with bi-polar disorder and HIV were more likely to report methamphetamine use, compared to those living with HIV only [42, 45]. In their analysis of Maryland Medicaid records, Chander et al found that people with SMI and HIV had a higher prevalence of chronic obstructive pulmonary disease, compared to people living with HIV alone but there were no differences between groups in the prevalence of other chronic diseases[40] .

In their study carried out among inpatients at two tertiary psychiatric hospitals in Uganda, Nakasujja et al (2012) found that people with SMI and HIV had worse overall cognition (at baseline and follow-up, after adjusting for sociodemographic characteristics) and across all domains (after adjusting for all other cognitive co-variates) compared to those with SMI only [32].Lastly, a small study found that people with

bi-polar disorder and HIV were more likely to be impaired across three out of four cognitive domains (visuospatial, recall, verbal recall performance), as compared to people with HIV alone [39].

Discussion

We found insufficient evidence to fully assess whether HIV and SMI have a syndemic effect. The overall number of studies identified was small. Although studies were generally high quality, there was heterogeneity in both selection of outcomes and choice of measure. It was therefore difficult to draw strong conclusions regarding the impact of co-morbid SMI and HIV across any outcome. Given that the health systems context is likely to be an important mediator of impact, the fact that almost all studies were carried out in the USA is a major limitation to generalisability of our findings. Nonetheless, our findings are important in terms of both highlighting gaps in the evidence-base, as well as providing an indication for future priority areas for research.

We found some evidence that SMI and HIV co-morbidity might be associated with elevated mortality: the two studies which compared mortality of people living with SMI and HIV with that of people living with HIV alone found that the co-morbid group had an increased risk of death. The study where people living with SMI alone were the comparison group found no evidence of a difference in risk between the co-morbid and the SMI-only group. The strongest evidence came from the highest quality study included in the review a Danish cohort using linkage of national registries of psychiatric illness and HIV (n=2,646,154). This study compared mortality for people living with schizophrenia and schizophrenia and HIV to people without either condition. Its findings were a greatly elevated mortality for both groups which was highest among people living with SMI and HIV, (MMR=76.5, 95% CI=44-122) compared to the general population [35]. Further research in settings outside of Denmark and the USA is necessary to explore the generalisability of these findings. It will be important to examine cause of death in order to understand the underlying mechanisms for the mortality findings.

We anticipated that our systematic review might reveal the impact of co-morbidity upon factors on the causal pathway to early mortality. However, evidence relating to navigation of the cascade of care, health service use, adherence and co-morbidities was scarce. There was a reasonable body of evidence examining various aspects of ART use (n=9). With the exception of two studies from Uganda, we found very little evidence of differences in navigation of the continuum of care between people living with co-morbid SMI and HIV and people living with HIV alone. Although the evidence base was sparser, results examining adherence to medical care comparing the co-morbid group with people living with SMI along seemed to suggest no difference between groups, whilst two studies suggested that those living with co-morbidity might have better outcomes than those living with SMI or HIV alone. Although symptoms associated with living with HIV and SMI might inhibit effective navigation of healthcare, in the USA, people living with HIV are eligible for support from various public programmes, which mean that the mental and physical healthcare services they access are more likely to be co-located [21]. Results of other studies carried out in the USA which suggested that people living with co-morbid SMI and HIV had elevated health service use and associated costs, as well as being less likely to have adverse social outcomes are consistent with this [25, 27, 30, 31]. Given differences in health systems, it is unlikely that results are generalizable to other settings. Differences are likely to be particularly stark for people living with co-morbid SMI and HIV in low income country settings where health systems are over-stretched and where those with SMI arguably experience greater stigma [50].

Finally, there was very little research regarding the prevalence and impact of mental and physical co-morbidities among people living with co-morbid SMI and HIV. There are several reasons why it is important to improve understanding in this area. Firstly, our research is consistent with the established evidence that suggests that co-morbid substance use is common among people living with SMI. The impact of this additional co-morbidity, including associations with social outcomes, is under-researched. Second, NCDs now account for the majority of deaths among both people living with HIV and those

living with SMI [51]. Third, both HIV treatment and treatment for SMI are associated with increased risk factors for NCDs [52, 53]. Finally, risk factors for NCDs among this population are likely to be modifiable as they are among the general population, albeit with additional complexity and barriers among this group. Our tentative findings that mortality may be elevated among the SMI and HIV group in some settings adds to the argument for NCDs to be a priority area for future research.

Our findings were limited by the size of the evidence-base. Heterogeneity of outcomes and measures eliminated the possibility of meta-analysis, meaning that uncertainty remains regarding the scale of increased risk for any outcome. Although we did not set limits based on language of publication, the fact that our search strategy is likely to only identify articles with an abstract published in English is a possible limitation of our design. Likewise, it is possible that we missed articles which were published in grey literature as this was not included in our searches. We feel that these limitations are unlikely to have had a significant impact upon findings.

Further research is necessary in order to understand the true impact of SMI and HIV upon physical and mental health and social outcomes and in order to assess whether this cluster of disease is syndemic. There are undeniable barriers to carrying out research among this group. We would therefore recommend that the best route forward for research in this area is to make use of study designs which use high quality routine data to explore relevant questions. Arguably, the growth of the use of health service records for research purposes makes this increasingly feasible. Gaining a better understanding of the problem across diverse settings and patient groups is an essential pre-requisite to the development of evidence-based guidelines for the management of co-morbid SMI and HIV. It will be important to explore differences between countries in future evidence syntheses, wherein an expanded evidence base may support meta-analysis to give a more definitive explanation about the extent to which the impact of co-morbidity differs by health system and sociocultural setting. Likewise, it will be

287 important to explore differences in impact across different mental disorder diagnostic groups. The need

288 for further research is therefore urgent, in order to improve the outcomes for this neglected group.

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Table 1: Study Eligibility Criteria

Table 2: Overview of Study Characteristics

Figure 1: PRISMA flow chart of Study Selection Process

Supplementary Digital Content:

Table S1: Results from studies comparing outcomes between people living with SMI and HIV and people living with SMI only

Table S2: Results from studies comparing outcomes between people living with SMI and HIV and people living with HIV only

Table S3: Search Strategy

Table 1. Study Eligibility Criteria

	Inclusion Criteria	Exclusion
Study Design	RCT, non-randomized controlled trials, cross sectional studies, cohort studies and case-control.	Case reports/series, editorials, opinion pieces, interviews, systematic reviews, or books.
Date of Publication	January 1983 to June 2017	Studies where data collection ended before January 1983
Language	All Languages	None
Type of Research	Quantitative	None
Study Population	Our population of interest is adults living with HIV and SMI. We only included studies which recruited: a) people with diagnosed HIV and SMI- (see criteria below) AND b) a control group- either: people living with SMI and no diagnosed HIV; OR, people living with HIV and no diagnosed SMI Definition of SMI: diagnosed according to either ICD10 or DSM V diagnostic categories. Definition includes: those illnesses which are associated with psychotic symptoms (schizophrenia and schizoaffective disorder), and bi-polar disorder: these are illnesses with a prolonged duration requiring long-term treatment; which are severe enough to result in significant disability (17). Definition of HIV: diagnosed with HIV	Adolescents/children under 18 years, diagnosis of Common Mental Disorder only (i.e. Depression without psychotic features, anxiety disorders).
Mental Health Outcomes	Mortality; suicidal ideation or attempts Health service use: inpatient admissions, outpatient visits; healthcare costs Mental health related: psychotropic medication use, adherence; cognition; symptom severity Co-morbidities: non-communicable diseases- cardiovascular disease, metabolic disorders, substance use, depression	None
Physical/HIV related Outcomes	Mortality Health service use: inpatient	Other outcomes

	admissions, outpatient visits; healthcare costs HIV-related: disease stage/severity - CD4 count, viral load, opportunistic infections; cognitive impairment/HIV-related dementia; ART use, initiation, adherence, discontinuation Co-morbidities: non-communicable diseases- cardiovascular disease, metabolic disorders, substance use, depression	
Social Outcomes	Functioning; housing; employment; stigma	Other outcomes

Table 2: Overview of Study Characteristics

Author and Year	Country	Study Design	Study Population	Number of Participants	Exposure	Mortality	Suicidality	AIDS-defining illness	ART* use/ discontinuation / adherence	Health service use, costs, receipt of care	Co-morbidity	Quality assessment (score 1-4, 4= highest quality)
Bansil et al. 2009	USA	Cohort (analysis of Data)	Inpatients (female)	5,901,621	Psychosis		✓					4
Blackstone et al. 2012	USA	Cross Sectional	Service-users	81	Bipolar disorder						✓	2
Bogart et al. 2006	USA	Cross Sectional	Service-users	880	SMI**				✓	✓		4
Chander et al. 2012	USA	Cohort (Retrospective)	Service-users	623	SMI	✓		✓			✓	4
Fremont et al. 2007	USA	Cross Sectional	Service-users	295	SMI					✓	✓	4
Helleberg et al. 2015	Denmark	Cohort (Population)	Service-users	2,646,154	Schizophrenia	✓			✓			4
Himelhoch et al. 2007	USA	Cross Sectional	Service-users	5119	SMI				✓	✓		4
Himelhoch et al. 2009	USA	Cohort (Retrospective)	Service-users	4989	SMI				✓		✓	4
Moore et al. 2012	USA	Cross Sectional	Service-users	73	Bipolar disorder				✓		✓	3
Nachega et al. 2013	Uganda	Cohort (Retrospective)	Outpatients	773	SMI			✓	✓			3
Nakasujja et al. 2012	Uganda	Cohort (Prospective)	Service-users	478	SMI						✓	3
Nurutdinova et al. 2012	USA	Cohort (Retrospective)	Service-users from	9003	Schizophrenia and Bipolar	✓		✓				4

			Veteran records		disorder							
Posada et al. 2012	USA	Cross Sectional	Service-users	72	Bipolar disorder			✓	✓		✓	1
Ronchi et al. 2000	Italy	Cross Sectional	Service-users	27	Psychosis				✓			1
Rosenberg et al. 2005	USA	Cohort (analysis of Data)	Service-users	777	SMI					✓		3
Rothbard et al. 2003	USA	Cohort (analysis of Data)	Service-users from Medicaid claims records	60503	SMI					✓	✓	3
Rothbard et al. 2009 a.	USA	Cohort (analysis of Data)	Service-users from Medicaid claims records	125027	SMI					✓		3
Rothbard et al. 2009 b.	USA	Cohort (analysis of Data)	Service-users from Medicaid Claims records	23729	SMI					✓		3
Walkup et al. 2001	USA	Cohort (analysis of Data)	Service-users from Medicaid Claims records	7744	SMI				✓			4
Wood et al 1997	USA	Cohort	Inpatients	322	SMI		✓					2

*ART= Antiretroviral Therapy

**SMI= Severe Mental Illness (in this case, schizophrenia, schizoaffective and bipolar disorder)

Figure 1. HIV and Serious Mental Illness: a syndemic ?